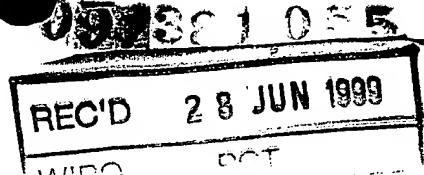


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The application was originally filed in English.

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For the Patent- and Registration Office

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NOVEL USE

The present invention relates to the use of certain pharmaceutical compounds as anti-inflammatory agents.

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Compounds having NMDA (N-methyl-D-aspartate) antagonist activity are known in the art, for example see Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

In particular certain compounds are disclosed in EPA 279937 as having NMDA antagonist

10 activity and are useful for treating various CNS disorders such as epilepsy and Parkinson's disease. In particular the compound known as remacemide is known from EPA 279937 as an NMDA antagonist and has also been shown to act as a sodium channel antagonist (Wamil et al., Epilepsy Research 23:1. 1996). It has now surprisingly been found that a metabolite of remacemide has activity in the carrageenan-induced inflammation model in the rat
15 hindlimb. As a result it is expected that compounds having NMDA antagonist activity and/or sodium channel antagonist activity will be useful for the treatment of inflammatory disorders.

20 In a first aspect the invention therefore provides the use of an NMDA antagonist and/or sodium channel antagonist for the treatment of inflammatory disorders.

Suitable NMDA antagonists include those listed in WO 94/13295 such as a) channel

blockers, i.e. antagonists which operate uncompetitively to block the NMDA receptor channel, b) receptor antagonists that compete with NMDA to act at the NMDA binding

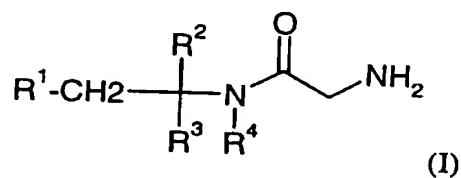
25 site, c) agents acting at either the glycine co-agonist site or any of the several modulation sites such as the zinc site, the magnesium site, the redox modulatory site, or the polyamine site, d) agents which inhibit the downstream effects of NMDA receptor stimulation such as agents which inhibit the activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism. Particular NMDA
30 antagonists useful in the invention include those disclosed by Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

Suitable sodium channel antagonists include those compounds disclosed by Taylor and Meldrum, Trends in Pharmacological Science, 16: 309. 1995.

Examples of preferred compounds include Cerestat (now called Aptiganel, Cambridge Neurosciences); Memantine (Merz) Riluzole (RPR); Lamotrigine; 4030W92 and 534U87 (all GlaxoWellcome); Phenytoin and Poshphenyltoin (Warner-Lambert), Carbamazepine and Oxcarbamazepine (Novartis); CNS-5161 and NPS-1506; Remacemide; eliprodil; 5 dexanabinol; SDZ-EAA-494; ARL-15896; CP-101606;

Particularly suitable compounds are those disclosed in EPA 279937, that is a compound of formula (I):

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where:

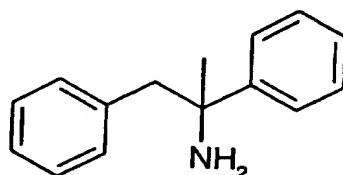
R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

15 R^4 is hydrogen or methyl;

and metabolites thereof both as free base and pharmaceutically acceptable salts thereof.

Preferably the compound of formula (I) is 2-amino-N-(1,2-diphenyl-1-methylethyl)acetamide (remacemide) or a metabolite thereof, most preferably the 20 compound known as 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof which has the following structure:



25

Suitable salts include all known pharmaceutically acceptable salts such as acid addition salts and preferably hydrochloride salts.

The invention also provides a method of treating or preventing inflammatory disorders which comprises administering to a patient a compound having NMDA antagonist activity or sodium channel antagonist activity or a pharmaceutically acceptable salt thereof.

- 5 Compounds which possess anti-inflammatory properties are useful in the prevention of clinical hyperalgesia and other pathologies associated with chronic pain such as neuropathies and joint inflammation. Particular inflammatory disorders which can be treated include arthritic conditions, eczema, psoriasis, dermatitis and other inflammatory conditions such as sunburn; inflammatory eye conditions such as uveitis and conjunctivitis;
- 10 lung disorders in which inflammation is involved such as asthma and bronchitis; conditions of the GI tract including aphthous ulcers, gingivitis, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, IBS, pyresis, pain and other damage to the GI tract, for example damage from infections by, for example, Helicobacter pylori, or treatments with non-steroidal anti-inflammatory
- 15 drugs.

In a further aspect the invention provides a compound having NMDA antagonist activity or sodium channel antagonist activity, in particular a compound of formula I or a metabolite thereof, in the manufacture of a medicament for use in the prevention or treatment of inflammatory disorders.

The invention also provides a compound having NMDA antagonist activity or sodium channel antagonist activity for the treatment or prophylaxis of inflammatory disorders. Suitable daily dose ranges are from about 1.0mg/kg to about 100 mg/kg. Unit doses may be administered conventionally once or more than once a day, for example, 2, 3, or 4 times a day, more usually 1 or 2 times a day.

The following example illustrates the invention.

Example 1

5 An inflammatory response was elicited in 12-13 day old Wistar rats by injection of 50 μ l of
carrageenan (0.5% in sterile physiological saline into the right footpad under brief
halothane anaesthesia). Paw oedema, a measure of the inflammation produced was
assessed by measuring dorsal-plantar thickness of both hind paws, using vernier calipers. A
difference score was generated by subtraction of the value for the non-injected paw from
that for the injected paw in each animal. Three baseline readings were taken at 90 min, 60
10 min and 30 min before application of test compounds. Measurements were made at 30 min,
1hr and thereafter at intervals of 1hr up to 6hr after carageenan application.

15 2,3-diphenyl-2-propylamine, dissolved in sterile physiological saline (0.9% NaCl w/v), was
administered in a dose of 75 mg/kg to six animals by intraperitoneal (i.p.) injection 30 min
prior to carrageenan injection. Control animals (n=6) received intraperitoneal injections of
vehicle alone, 30 min before injection of carrageenan.

20 Data were expressed as mean \pm SEM and plotted as a function of time. Statistical analysis
was performed using an ANOVA analysis of the areas under the curves, followed in the
case of significant difference ($p<0.05$) by student's unpaired t-test analysis at individual
time points.

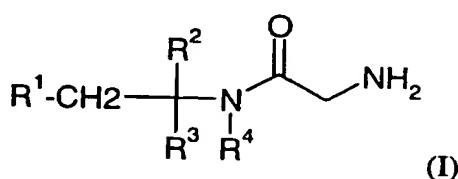
25 Intraplantar injection of carageenan resulted in the development of paw oedema, with a
duration >6hr and which peaked at 4hr post application. Pretreatment with 2,3-diphenyl-2-
propylamine, 75 mg/kg i.p. significantly ($p<0.05$) reduced the extent of paw oedema
elicited at 2hr, 3hr and 4hr after carageenan treatment, compared with application of the
drug vehicle alone.

CLAIMS

1. Use a compound having NMDA antagonist activity or sodium channel antagonist activity for the treatment of inflammatory disorders.

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2. Use according to claim 1 where the compound having NMDA antagonist activity or sodium channel antagonist activity is a compound of formula (I):



10

where:

R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

R^4 is hydrogen or methyl;

15 and metabolites thereof both as free base and pharmaceutically acceptable salts thereof.

3. Use according to claim 1 or 2 where the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

20 4. Use according to claim 1 or 2 where compound is 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof.

25 5. A method of treating or preventing inflammatory disorders in a mammal which comprises administering a compound having NMDA antagonist activity or sodium channel antagonist activity or a pharmaceutically acceptable salt thereof.

Inl. t Patent- och reg.verket

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ABSTRACT

The invention relates to the use of certain pharmaceutical compounds as anti-inflammatory agents.

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